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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,811	05/04/2006	Philipp E. Scherer	21580YP	8553

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EXAMINER	
RIDER, LANCE W	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,811	SCHERER ET AL.	
	Examiner	Art Unit	
	LANCE RIDER	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

The remarks and amendments filed on March 12th 2010 are acknowledged. Claims 1-21 are amended.

Response to arguments

Withdrawn Rejections

Receipt and consideration of Applicants' amended claim set and remarks filed on March 12th 2010 is acknowledged. Rejections and objections not reiterated from previous office actions are hereby withdrawn. The following rejections or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Response to Applicant's Arguments Regarding Above Rejections

Rejection of claims 1-21 under 35 U.S.C. 103(a) as being unpatentable over Hirose, H., et al., (Metabolism, 2002) in view of Tsao, T., et al., (Journal of Biological Chemistry, 2002), Hackeng, W.H.L., et al., (Journal of Clinical Endocrinology and Metabolism, 1986), Furuya, Y., et al, (International Journal of Urology, 2000), and Lemieux, I., et al., (Archives of Internal Medicine, 2001)

Applicant's arguments, starting on page 8, of the reply filed on March 12th 2010 with respect to the following rejections under 35 USC 103(a) have been fully considered but are not found persuasive:

Applicant argues the following:

1) Hirose does not teach measurements of adiponectin within 4 weeks.

2) Hirose does not suggest that adiponectin is a marker for diabetes and would allow for monitoring the effectiveness of the diabetic drug ploglitazone.

3) Tsao does not teach that the HMW or LMW adiponectin have different effects in diabetic patients or on diabetes.

4) Hackeng, Furuya, and Lemieux do not teach ratios of adiponectin.

In response to applicant's argument 1, the new rejection based upon Hirose and Yu, both of whom teach adiponectin measurements as assays for measuring a patient's response to a diabetes treatment teaches a measurement window of 2 weeks to 3 months, meeting the instantly claimed limitation of less than 4 weeks, and rendering this modification of the claims obvious.

In response to applicant's argument 2, Hirose teaches measuring adiponectin levels in diabetic patients before and after their treatment with a diabetes drug. Hirose teaches that serum levels of adiponectin are low in diabetic patients and raise after treatment with anti-diabetic drugs. (see page 314, paragraph 4, and the abstract.)

In response to applicant's argument 3, Tsao specifically teaches that full length adiponectin increases the ability of insulin to suppress hepatic glucose production. (See

page 29362, paragraph 1.) Tsao also teaches that adiponectin and serum concentrations are altered in diabetic patients, change in response to anti-daibetes drugs, and effect insulin resistance. (See page 29359, paragraph 2.) As well the link between NF-kB activation and insulin resistance and diabetes has long been known. See (Yuan, M., et al., Science, 2001, paragraphs 1-3.) provided as evidence of the known connection between NF-kB and diabetes and insulin resistance.

New Grounds of Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The new grounds of rejection is based on applicant's amendment of claims 1-21 changing the scope of the claims to require testing for a change in adiponectin within 4 weeks after administration of a drug.

Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hirose, H., et al., (Metabolism, 2002) in view of Yu, J.G., et al., (Diabetes, 2002), Tsao, T., et al., (Journal of Biological Chemistry, 2002), Hackeng, W.H.L., et al., (Journal of Clinical Endocrinology and Metabolism, 1986), Furuya, Y., et al, (International Journal of Urology, 2000), and Lemieux, I., et al., (Archives of Internal Medicine, 2001).

Hirose teaches a method for determining the effects of a drug on metabolic parameters in diabetic patients. The study shows the positive steps of measuring the total concentration of the serum marker adiponectin in diabetic patients before a treatment. The patients were then treated with pioglitazone. Pioglitazone is a PPAR-gamma agonist with a TDZ structure meeting the limitations recited in instant claims 9-11. The patients total serum adiponectin levels were then measured 3 months after

commencement of the pioglitazone treatment. It is also taught that adiponectin levels increased during treatment with the diabetes therapy pioglitazone (a thiazolidinedione), thus showing that an increase in total adiponectin levels correlate with a response to a diabetes therapy. (See page 315, paragraph 3, and page 316, figure 1.)

Hirose does not teach measuring the adiponetcin levels of a subject at less than 4 weeks.

Yu teaches treating diabetic subjects with troglitazone (a diabetic drug of the thiazolidinedione class) and measuring their adiponectin levels after 2 weeks. (See page 2973, paragraph 2.)

Together Hirose and Yu teach using serum adiponectin as a marker in assaying the response of diabetic subjects to drugs over a time range from 2 weeks to 3 months. A range can be disclosed in multiple prior art references instead of in a single prior art reference depending on the specific facts of the case. Iron Grip Barbell Co., Inc. v. USA Sports, Inc., 392 F.3d 1317, 1322, 73 USPQ2d 1225, 1228 (Fed. Cir. 2004). The range disclosed by Hirose and Yu overlaps with the instantly claimed “less than 4 weeks”. In the case where the claimed ranges “overlap or lie inside ranges disclosed by the prior art” a prima facie case of obviousness exists. In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). Thus in the instant case the prior art renders obvious the "less than 4 weeks" recited in the instant claims.

Hirose and Yu do not teach the measurement of HMW adiponectin or its ratio to the total or LMW adiponectin levels.

Tsao teaches the measurement of HMW adiponectin (Acrp30) and that HWM adiponectin is the active version of adiponectin. It is reported in the abstract and throughout the disclosure that the HMW form of adiponectin and not the LMW form is responsible for the biological activity of adiponectin, specifically its function in the biological activation of NF-kB signaling. Tsao also indicates that the distribution (ie. ratio) of the HMW and LWM forms of adiponectin may be biologically important. (See page 29359, paragraph 3). Tsao indicates a reason for measuring just the HMW adiponectin levels, as HMW adiponectin is the biologically relevant species of adiponectin.

Tsao does not indicate measuring the ratio of HMW to total or LMW adiponectin for this particular disease marker.

Hackeng, Furuya, and Lemieux teach methods for measuring important serum markers. Hackeng teaches the measurement of the ratio of intact to total parathyroid hormone as a measurement in diagnosis and treatment of parathyroid disorders. Hackeng specifically states that measuring both the “individual maker”, intact parathyroid hormone and the total “class” of parathyroid hormone is more specific and sensitive than measuring the class of the marker alone. Furuya (International Journal of Urology, 2000) teach the measurement of free to total prostate specific antigen as a measurement in the diagnosis and treatment of prostate cancer. Lemieux (Archives of Internal Medicine, 2001) teach the measurement of total cholesterol versus HDL cholesterol or LDL versus HDL cholesterol as a measurement in the diagnosis and treatment of heart disease. All of these references teach the measurement of a ratio of

the total amount of a disease marker to its active portion. By measuring the ratio of the total amount of the disease marker, “the class”, to the active portion of the disease marker, “the individual”, these studies show greater specificity and sensitivity than measuring just the class of the disease markers provides. It was therefore common practice for the skilled artisan at the time of the invention to measure ratios between the class and individuals of that class for many different disease markers.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Hirose and Yu with the teachings of Tsao and those of Hackeng, Furuya, and Lemieux in order to provide an improved assay for diabetes (insulin resistance). Methods for determining the response of a patient to therapies for insulin resistance by measuring total adiponectin were known. It was also known that HMW adiponectin was the active species for this "class" of markers. As it was common practice in the art to measure ratios between the class of a disease marker and the biologically important individuals of that class, measuring the ratio between total adiponectin and its biologically important individual would have been obvious to the skilled artisan. In addition as Hackeng specifically teaches that measuring the ratios between the class and individuals of that class for disease markers increases the accuracy of such assays, the skilled artisan would have been further motivated to make this combination in order to improve the already known assay measuring total adiponectin.

The artisan would also have had a reasonable expectation of success since the assays for measuring both total and HMW adiponectin were already used for measuring serum adiponectin.

Clams 3-8, and 13-21 are drawn to a method in which the patient is determined to be a responder based upon the change in the HMW to the total adiponectin ratio at set time periods after treatment commences. Determining such a threshold where one determines a patient is a responder is a mental process. It was already known that an increase in total adiponectin correlated with a response to insulin treatment. As such the skilled artisan was already capable of determining when a patient was responding to treatments based upon changes in total adiponectin levels. Finding a corresponding threshold for the ratio of HMW to total adiponectin would follow the same mental process. For those of ordinary skill in the art, such as diagnosticians, it was common practice to determine when patients were responding to a therapy. Such determinations are based upon many factors such as the age, weight, size, gender, and extenuating medical conditions present for each patient, all of which were common factors used in such diagnosis.

. "[W]here the general conditions of a claim are taught in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In the instant case methods of measuring ratios of adiponectin levels and determining a patient's response to therapeutic treatment based on those levels were well known in the art at the time of the invention. The specific threshold of such ratios at which a patient was considered to

be responsive to such a treatment were not specifically taught, but the determination of a threshold at which a patient was responding to a treatment would have common practice for those of skill in the art at the time of the invention.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LANCE RIDER whose telephone number is (571)270-1337. The examiner can normally be reached on M-F 11-12 and 1-4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LANCE RIDER/
Examiner, Art Unit 1618

/Eric E Silverman/
Primary Examiner, Art Unit 1618